

hereby authorized to charge said fee to Arnold, White & Durkee deposit account No. 01-2508/UTSC:584/PAR.

Please amend the Application as follows:

IN THE CLAIMS

Cancel without prejudice claims 10 through 29 and 32 through 51.

Claim 1, line 1, delete "A" and insert therefore -- An --.

Claim 2, line 2 after "a" insert -- non-lipid --.

Please add the following new claim:

52. The submicron-reconstitute preliposome-lyophilate of Claim 1, said preliposome-
lyophilate being halogenated solvent-free.

REMARKS

I. STATUS OF THE CLAIMS

Claims 1 through 9 are pending.

Claims 10 through 29 and 32 through 51 have been withdrawn from consideration, and now canceled.

Claims 1 through 9 are rejected.

II. AMENDMENTS

Claim 1 has been amended to replace "a" with "an" to correct a grammatical error.

Claim 2 has been amended to note that the surfactants claimed are non-lipid surfactants.

This amendment is supported throughout the Application with particular reference to Page 1, lines 25 and 28, wherein in describing the use of surfactants ("The use of less than 4% surfactant has been reported to yield stable liposomal preparations.") it is made clear that the lipid of a mixture leading to a lipid film for forming a liposome is not considered surfactant. Similarly,

page 2, lines 4-9, 10-13, and page 5, lines 8 and 9 (no surfactant liposomes), and Claim 7, (surfactant as a percentage relative to lipid). At page 4, lines 25 to 27, surfactant is defined as anionic, cationic or nonionic, and preferably a Tween surfactant.

Claims 10 through 29 and 32 through 51, having been withdrawn from consideration, are canceled without prejudice. Applicants' make explicit that cancellation is made only in response to the restriction requirement and for no other reason. Applicants intend to pursue the subject matter of these claims in a continuing application.

Claim 52 has been inserted and contains a limitation to a lyophilate absent halogenated solvent. Support for this amendment is found throughout the Specification with particular reference to page 10, lines 13 and 14.

III. RESTRICTION OR ELECTION REQUIREMENT

Applicant notes election of Group I corresponding to Claims 1 through 9. It is further noted that, despite Applicants' traverse, the restriction is maintained. Further comment is deemed unnecessary.

IV. REJECTION UNDER § 112, SECOND PARAGRAPH

Claims 1 through 9 are rejected under § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

As noted by the Examiner in the Office Action of November 24, 1998, page 2, Claims 1 through 9 are drawn to an aqueous/t-butanol solvent system/lyophilized powder.

In response to the questions posed by the Examiner in the Office Action of March 17, 1999, at the bottom of page 2 as to what is being claimed, a lyophilized powder is being claimed.

With reference to Claim 1, the Examiner's attention is respectfully drawn to page 10 of the Specification.

At lines 9 through 17, the phrase "aqueous/t-butanol solvent-system" is defined with reference to a preliposomal lyophilate. "Aqueous/t-butanol solvent-system" is a reference to a specific method of preparation of the lyophilate. The term also encompasses a limitation as to solvent residues in the lyophilate.

At lines 19 through 23, the term "facile-reconstitute" is defined with reference to a preliposomal lyophilate. Facile-reconstitute describes a defining physical property of the novel lyophilate – its behavior upon reconstitution.

At line 24 and continuing to page 11, line 2, the term "submicron-reconstitute" is defined with reference to a preliposomal lyophilate. "Submicron-reconstitute" describes a defining physical property of the novel lyophilate – its behavior upon reconstitution.

Claims 2 through 9 are dependent on Claim 1. Claims 2 through 9 further define the specific elements noted above. It is submitted that Claims 1 through 9 are in compliance with § 112, second paragraph.

V. REJECTION UNDER § 102(b)

Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. § 102(b), as anticipated by US 4,950,432 to Mehta et al. ("Mehta '432"). This rejection is respectfully traversed.

A. Applicants' Invention

Claim 1 is directed to a preliposomal lyophilate that is

- (i) aqueous/t-butanol solvent-system -- a description of its method of preparation,

- (ii) facile-reconstitute -- a distinct physical characteristic of the lyophilate as to the behavior upon reconstitution or hydration, and
- (iii) submicron-reconstitute -- a distinct physical characteristic of the lyophilate as to the behavior or result upon hydration and suspension.

As these limitations are defined in the Specification, the lyophilate of Claim 1, arises from an aqueous/t-butanol solvent-system. Further, the lyophilate has substantially no trace of organic solvent other than t-butanol, and t-butanol is present at less than about 0.01%. The claimed lyophilate is fully reconstituted with hand-shaking in about 1 minute to obtain liposomes of about 400nm or less. And finally, the lyophilate produces liposomes of submicron size (diameter) distribution upon reconstitution into liposomes in the presence of aqueous solution, *i.e.*, submicron-reconstitute.

Claim 2 requires a surfactant. As Claim 2 has been amended, Applicants make clear that the required surfactant is not a lipid.

Claims 8 and 9, dependent on Claim 2 include limitations as to the amount of surfactant.

B. The Disclosure of Mehta '432

In raising Mehta '432, the Examiner draws attention to the Abstract, as well as columns 6 and 7, the Examples, and the claims.

Solvents -- Reference to the Abstract discloses dissolving phospholipids in a "first solvent" and a "second solvent" and there after employing a t-butanol methylene chloride mixture as a third solvent. Attention is drawn to step in Example 1 (col. 6, lines 53-66) wherein the various organic solvents were subjected to partial vacuum evaporation at 40° C, reconstitution in t-butanol, and overnight lyophilization. A generally similar solvent evaporation process (employing chloroform as one solvent) was conducted in Example 2 (col. 8, lines 25-41).

Col. 6, lines 1 through 25, teach the use of methanol and chloroform as first and second solvents. Further, as noted in the abstract, t-butanol is used as a solvent as a mixture with methylene chloride.

Reconstitution -- Col. 8, lines 1 through 5, disclose heating the lyophilate to 40° C as an element of reconstitution. Col. 8, lines 42 to 44, note that when the lyophilate and a diluent were mixed "liposomes did not form until the suspension was warmed in a water bath at about 40° C for about 2-5 minutes."

Liposome size -- Reconstitution, in each instance, is described as associated with filtering the reconstituted material through a submicron filter. Col. 7, lines 60-62 and col. 7, lines 34-36. Note that the t-butanol mixture is also filtered. Abstract, and col. 6, lines 20-25.

C. The Deficiencies of Mehta '432

Different Solvent System/Retained Solvent Residues -- Mehta '432 requires "first solvent" and a "second solvent" and there after employing a t-butanol methylene chloride mixture as a third solvent. This is not the claimed aqueous/t-butanol solvent-system. Further, given the solvent system of Mehta '432, the required condition that the lyophilate have substantially no trace of organic solvent other than t-butanol, Mehta '432 is not met. It is submitted that mere evaporation and lyophilization is inadequate in solvent removal.

Labored Reconstitution -- The claimed lyophilate is defined as distinct from that of Mehta '432 by the behavior of the lyophilate upon reconstitution. As claimed, the facile-reconstitute lyophilate will fully reconstitute with hand-shaking in about 1 minute, to obtain liposomes of about 400nm or less. The lyophilate of Mehta '432 will not form liposomes until the suspension is warmed in a water bath at about 40° C for about 2-5 minutes." Col. 8, lines 42-44. The lyophilate of Mehta '432 is utterly distinct from the claimed lyophilate.

Submicron Liposomes -- Mehta '432 requires submicron filtration to attain submicron liposomes. Col. 7, lines 60-62 and col. 7, lines 34-36. Again, note that the t-butanol mixture is also sized by filtration. Abstract, and col 6, line 20-25. Thus, Mehta '432 does not anticipate any of the above-noted limitations of Claim 1.

Mehta '432 does not teach the use of surfactants. Thus, Mehta '432 does not anticipate the surfactant limitation of Claim 2. Similarly, as no surfactants as required by Claim 2 are found within Mehta '432, Mehta '432 cannot anticipate Claims 8 or 9 as to percentages of such surfactants.

VI. REJECTION UNDER § 102(e)

Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. § 102(b), as anticipated by US 5,811,119 to Mehta et al. ("Mehta '119"). This rejection is respectfully traversed.

A. The Disclosure of Mehta '119

In raising Mehta '119, the Examiner draws attention to the Abstract , Columns 6 and 7, and the Examples.

Solvents -- Nothing in Mehta '119 discloses the claimed aqueous/t-butanol solvent-system. The sole solvent disclosed in Mehta '119 is t-butanol. Col. 7, lines 23 and 24, and Example 1 (col. 7, lines 54-61).

Reconstitution -- Example 1 (col. 7, line 66 through col. 8, line 8) describes a reconstitution regimen of one minute of hand shaking "to obtain a preparation devoid of any aggregates or clumps. Example 8 discloses reconstitution by vortexing (not hand shaking) for 2-3 minutes. Col. 20, lines 44 through 49.

Liposome size -- Reconstitution of the lyophilate of Mehta '119 is clearly defined as larger than submicron. Example 1 (col. 8 lines 18 through 21); similarly, Example 8 (col. 20,

lines 44 through 49). Vortexing (not hand shaking) for 2-3 minutes yielded liposomes with an average diameter of 3.1 • m.

C. The Deficiencies of Mehta '119

Different Solvent System -- Mehta '119 discloses no more than the use of t-butanol. This is not the claimed aqueous/t-butanol solvent-system.

Labored Reconstitution -- The claimed lyophilate is defined as distinct from that of Mehta '119 by the behavior of the lyophilate upon reconstitution. As claimed, the facile-reconstitute lyophilate will fully reconstitute with hand-shaking in about 1 minute to obtain liposomes of about 400nm or less. The lyophilate of Mehta '119 will not form submicron liposomes when shaken (clumps removed) and requires vortexing for 2-3 minutes. This is distinct from the claimed lyophilate.

Submicron Liposomes -- Mehta '119 reports the size micron or more of the resulting liposomes. It is explicit from the data of Mehta '119 that the claimed submicron limitation is not met. Thus, Mehta '119 does not anticipate any of the above-noted limitations of Claim 1.

Mehta '119 does not teach or suggest the use of surfactants. Thus, Mehta '119 does not supply the surfactant limitation of Claim 2. Similarly, as no surfactants as required by Claim 2 are found within Mehta '119, Mehta '119 cannot anticipate Claims 8 or 9 as to percentages of such surfactants.

VII. REJECTION UNDER § 103(a)

Claims 3 through 9 are rejected under 35 U.S.C. § 103(a), as obvious in view of either Mehta '432 or Mehta '119 as cited above and further in view of US 5,585,12 to Unger ("Unger"), US 5,089,602 to Isliker (Isliker) and US 5,653,996 to Hsu ("Hsu") individually or in combination. This rejection is respectfully traversed.

A. Applicants' Invention

Claim 3 of the instant invention is dependent on Claim 2 and drawn to the broad aspect of a preliposomal lyophilate containing anionic, cationic or nonionic surfactant. Claim 4 dependent on Claim 3, specifies nonionic surfactant. Claim 5 dependent on Claim 4 specifies Tween as the surfactant. Claim 6 dependent on Claim 5 specifies Tween 20. Claim 7 dependent on Claim 6 specifies surfactant from about 4 mole % to about 2 mole % of the lipid content of the lyophilate. Claims 8 depends from Claim 2 and specifies surfactant from about 4 mole % to about 0.1 mole % of the lipid content of the lyophilate, and Claim 9 dependent on Claim 8 cites from about 4 mole % to about 2 mole %.

B. Teaching of Mehta '432

The comments on the teaching of Mehta '432 as noted above are reiterated. Further, Mehta '432 does not teach or suggest any claimed surfactant, and specifically makes no mention of Tween, Tween 20 or any ratios of surfactant to lipid. Mehta '432 makes no note of the stability or instability of liposomes resulting from the lyophilate.

C. Deficiency of Mehta '432

Different Solvent System/Retained Solvent Residues -- Claims 3 through 9 retain the limitations of Claims 1 and 2. As note in relation to Claim 1, Mehta '432 requires "first solvent" and a "second solvent" and there after employing a t-butanol methylene chloride mixture as a third solvent. This is not the claimed aqueous/t-butanol solvent-system, and nothing within Mehta '432 teaches or suggests the claimed solvent system. Further, given the solvent system of Mehta '432, the required condition that the lyophilate have substantially no trace of organic solvent other than t-butanol is not met. It is submitted that mere evaporation and lyophilization is inadequate in solvent removal to the required level. Labored Reconstitution -- The claimed lyophilate of Claims 3 through 9 is defined as distinct from that of Mehta '432 by the behavior of

the lyophilate upon reconstitution. As claimed, the facile-reconstitute lyophilate will fully reconstitute with hand-shaking in about 1 minute, to obtain liposomes of about 400nm or less. The lyophilate of Mehta '432 will not form liposomes until the suspension was warmed in a water bath at about 40° C for about 2-5 minutes.” Col. 8, lines 42-44. This is utterly distinct from the claimed lyophilate, and nothing in Mehta '432 suggests a lyophilate that would meet the limitation for facile-reconstitution.

Submicron Liposomes -- Mehta '432 requires submicron filtration to attain submicron liposomes. Col. 7, lines 60-62 and col. 7, lines 34-36. Again, note that the t-butanol mixture is also filtered. Abstract, and col 6, line 20-25. Mehta '432 does not teach or suggest the claimed submicron-reconstitute lyophilate of Claims 3 through 9.

No Surfactants – As amended, Claims 3 through 9 are dependent on Claim 2 which defines the claimed surfactant claimed as a non-lipid surfactant. As the Examiner notes, Mehta '432 does not teach or suggest any claimed surfactant, and specifically makes no mention of Tween, Tween 20 or any ratios of surfactant to lipid. Nothing in Mehta '432 can provide the missing elements of Claims 3 through 9. Thus, Mehta '432 cannot render any of Claims 3 through 9 obvious.

D. Teaching of Mehta '119

The comments on the teaching of Mehta '119 as noted above are reiterated. Further, Mehta '119 does not teach or suggest any claimed surfactant, and specifically makes no mention of Tween, Tween 20, or any ratios of surfactant to lipid. The stability of liposomes resulting from the lyophilate were determined to be “80% stable over the period if the experiment, even in the presence of 20%” fetal calf serum (Col. 8, 62-64) thus improved stability would not be a perceived need for Mehta '119.

E. Deficiency of Mehta '119

Different Solvent System -- Claims 3 through 9 retain the limitations of Claims 1 and 2.

Mehta '119 discloses no more than the use of t-butanol. This is not the claimed aqueous/t-butanol solvent-system of Claims 3 through 9 as dependent on Claim 1.

Labored Reconstitution -- The claimed lyophilate of Claim 1, and therefore of Claims 3 through 9, is defined as distinct from that of Mehta '119 by the behavior of the lyophilate upon reconstitution. As claimed, the facile-reconstitute lyophilate will fully reconstitute with hand-shaking in about 1 minute, to obtain liposomes of about 400nm or less. The lyophilate of Mehta '119 will not form submicron liposomes when shaken. This is distinct from the claimed lyophilate.

Submicron Liposomes -- Mehta '119 reports the size of the resulting liposomes. It is explicit from the data of Mehta '119 that the claimed submicron limitation is not met. Thus, Mehta '119 does not supply any of the above-noted limitations of Claim 1.

No Surfactants – As the Examiner notes, Mehta '119 does not teach or suggest the use of surfactants. Thus, Mehta '119 does not supply the surfactant limitation of Claim 2. Similarly, as no surfactants as required by Claim 2 are found within Mehta '119, Mehta '119 cannot anticipate Claims 8 or 9 as to percentages of such surfactants.

For the above noted reasons, Mehta '119 cannot render the instant invention obvious.

F. The Teaching of Unger

The Examiner cites Unger as teaching that “non-ionic detergents such as Tweens stabilize the liposome compositions,” and cites Unger, col. 25, lines 38-48 (emphasis added). Unger represents an example of a basket type disclosure as defined in *In re Rushig et al.*, 154 U.S.P.Q. 118 (CCPA 1967).

It is an old custom in the woods to mark trails by making a blaze on trees. It is no help in finding a trail or in finding one's way through the woods where the trails

have disappeared -- or have not yet been made, which is more likely the case here -- to be confronted simply by a large number of unmarked trees. *In re Rushig et al.*, 154 U.S.P.Q. 122.

Unger provides an extensive litany of possibilities, but only Unger, Example 10, (col. 43, line 45 to col. 44, line 10) employs both lyophilization and surfactant. Unger, Example 10, tests both 1mole % and 5 mole % detergent. The smallest liposomes produced in Example 10 is 6 • m – without regard to the amount of surfactant.

To reconstitute the lyophilate of Example 10, Unger teaches vortexing for 10 minutes. Col 43, lines 58,59. Identical vortexing is employed in Unger, Example 7, the only other lyophilization example of Unger. Col. 42, lines 51, 52.

G. The Deficiency of Mehta '432 or Mehta '119 in view of Unger

Applicants claim a submicron facile-reconstitute preliposomal powder derived from an aqueous/t-butanol solvent system. Neither Mehta '432 nor Mehta '119 supply these elements. Unger does not teach or suggest any of these conditions. Unger does not mention t-butanol. Unger teaches away from the sub-micron condition in specifying that only larger liposomes were produced when detergent was employed. Unger teaches only lengthy vortex reconstitution of detergent containing liposomes. A reference which leads of away from the claimed invention cannot render it unpatentably obvious. Dow Chem. Co. v. American Cyanamid. Co., 2 U.S.P.Q. 2d 1350 (Fed.Cir. 1987). Unger clearly teaches away as to both submicron reconstitution and facile-reconstitution. The Examiner offers *increased stability* of liposomes upon reconstitution or the claimed preliposomal powder as a reason to combine the teachings of Unger as to surfactants with either Mehta '432 or Mehta '119. “Stability” at a specific level -- whether increased or decreased -- is a quality and cannot be evaluated as a motivation to combine absent a context. The claimed material is a preliposome lyophilate, and not a liposome. The “increased stability”

offered by incorporation of surfactant as taught by Unger does teach increasing the stability of this lyophilate. To provide motivation for combination, there must be some teaching that the product of one of the Mehta references would need increased stability. This has not been offered by the Examiner nor noted in either Mehta reference. If the Examiner has a documentary basis or is of the opinion that such motivation is present, the Examiner is respectfully requested to provide documentation or an affidavit under 37 C.F.R. § 107(b).

It is well settled that the mere fact that mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. ACS Hospital Systems, Inc. v. Montefiore Hospital 221 U.S.P.Q. 929 (Fed.Cir. 1984). Neither Mehta '432 nor Mehta '119 note that stability is a problem with the liposomes disclosed in either reference. Thus, combining Unger with either Mehta '432 or Mehta '119 is necessarily improper hindsight reconstruction of the Applicants' invention in the light of Applicants' disclosure.

To combine, it is respectfully submitted that the Examiner is improperly picking and choosing features contrary to the teachings of Unger. While Unger notes that surfactants may be used and that liposomes may be made in submicron sizes, the only teaching of Unger as to surfactant-containing liposomes is explicit that "the smallest size detected is about 6 • m -- without regard to surfactant concentration. The Examiner's attention is respectfully drawn to col. 43, lines 61-65, (1mole% surfactant) and col 42, line 65 to col. 44, line 2 (10 mole % surfactant). The teaching of Unger on reconstitution in either example of lyophilization (Examples 7 and 10) is that vortexing for 10 minutes is required. Thus, the teaching of Unger is that the use of surfactants and lyophilization -- while possible -- leads to large liposomes with vortexing required for reconstitution. Unger is not properly combined with either Mehta '432 or Mehta '119. The combination of Unger with either Mehta '432 or Mehta '119, as taught by Unger will

lead to a lyophilate that is not facile-reconstitute which will produce multi-micron liposomes contrary to that which is claimed. Finally, not one of these three references discloses the claimed solvent system.

H. The Teaching of Isliker

Isliker is cited by the Examiner as teaching that Tweens can be used in the preparation of liposomes which are then lyophilized, Example 11. A close reading of Isliker, Example 11 discloses that the detergents used are removed from the process at an early stage, and no detergent containing preliposomal lyophilate is taught or suggested by Isliker. Example 11, step a) directs the addition of detergent at col. 8. line 46, and the removal of detergent at lines 47-55.

I. The Deficiency of Isliker.

Isliker does not teach or suggest the use of Tween or any other surfactant except as found within an intermediate processing step. No detergent containing lyophilate is taught or suggested by Isliker. No aqueous/t-butanol solvent system is taught or suggested by Isliker. Neither facile-reconstitute liposomes nor submicron liposomes are taught or suggested by Isliker. Nothing in Isliker supplies any deficiency of Mehta '432, Mehta '119 or Unger. The present invention cannot be rendered obvious by the combination of references.

J. The teaching of Hsu

Hsu is cited as teaching that Tweens can be used in the preparation of liposomes which are then lyophilized. Col. 5, lines 25 *et seq.* Attention is drawn to col. 11, line 42 through col. 12 line 2, that submicron liposome size is achieved through “sizing” methods such as sonication and extrusion.

K. Deficiency of Hsu

Applicants claim a sub-micron facile-reconstitute preliposomal powder derived from an aqueous/t-butanol solvent system. Neither Mehta '432 nor Mehta '119 supply these elements.

Hsu does not teach or suggest any of these conditions. Hsu does not teach or suggest the claimed solvent system. Hsu states that Tweens can be employed in liposomal preparation. Hsu is no more than a mere basket disclosure, offering but a single element -- a surfactant -- of the claimed preliposomal lyophilate. Applying Hsu to the present combination is respectfully submitted to be improper hindsight application. No reference offers the required solvent system. No reference teaches the product displaying the element of facile-reconstitution at submicron sizes. And even if applied, no combination of Mehta '432 or Mehta '119 with any or all of Unger, Isliker, or Hsu arrive at the claimed invention.

The Examiner offers that “[i]n essence, the secondary references all teach the *routine practice in the art* of the use of Tweens in liposomal preparations” (emphasis added). This is the type of hindsight which the Court in In re Dembiczak 50 U.S.P.Q. 2d 1614 (Fed.Cir. 1999) explicitly held to be improper.

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. 50 U.S.P.Q. 2d 1617 (citations omitted).

In criticizing the decision below, the Court in Dembiczak states:

Nowhere does the Board particularly identify any suggestion, teaching, or motivation to combine the . . . [various] references, nor does the Board make specific--or even inferential--findings concerning the identification of the relevant art, the level of ordinary skill in the art, the nature of the problem to be solved, or any other factual findings that might serve to support a proper obviousness analysis. To the contrary, the obviousness analysis in the Board's decision is limited to a discussion of the ways that the multiple prior art references can be combined to read on the claimed invention. 50 U.S.P.Q. 2d 1618, 1619.

In the present matter, the Examiner opines on the level of skill in the art, and the ways that the multiple prior art references can be combined to read on the claimed invention. Presuming (*arguendo*) that the Examiner's view of the state of the skill in the art were accurate, it is respectfully submitted that the reasoning offered is insufficient. Nothing is offered as to the nature of the problem to be solved. The sole reasoning offered by the Examiner as to the combination of Unger with Mehta '432 or Mehta '119 is to improve stability. As noted above, that motivation is unsupported speculation of the Examiner suggesting the combination would be desirable to combine in Mehta '432 or Mehta '119. The Examiner has pointed to nothing within the Mehta '432 or Mehta '119 references (or indeed by the Applicants) to substantiate this assumption.

Further more, no combination of references can be combined to arrive at the claimed product of an aqueous/t-butanol solvent-system substantially no trace of organic solvent other than t-butanol and that t-butanol is present at less than about 0.01%.
fully reconstituted with hand-shaking in about 1 minute to obtain liposomes of about 400nm or less. Note that Mehta '432 specifically requires heating and Mehta '119 requires vortexing and yields large liposomes (3.1 • m).

Claim 3 of the instant invention is dependent on Claim 2 and drawn to the broad aspect of a preliposomal lyophilate containing anionic, cationic or nonionic surfactant. Of the three references offered to provide the surfactant element --

Unger teaches away as to liposome size and reconstitution facility.

Isliker is deficient in failing to disclose detergent containing lyophilate.

Hsu is no more than a mere basket disclosure, offering but a single element -- a surfactant -- of the claimed preliposomal lyophilate without solvent system or any reason to

combine the necessary elements.

Claim 4, specifies nonionic surfactant, and Unger, Isliker or Hsu can no more provide these elements to Mehta '432 or Mehta '119 than they could to Claim 3. Similarly , Claim 5 which specifies Tween as the surfactant; Claim 6 which specifies Tween 20, and Claim 7 which specifies surfactant from about 4 mole % to about 2 mole % of the lipid content of the lyophilate cannot be obviated by the offered combination of references. As to Claims 7, 8 and 9, while Unger notes 1 mole % detergent, as noted above, the entirety of the teaching comprises elements teaching away from and inconsistent with the claimed invention. Isliker and Hsu offer no amounts of the surfactant to provide the claimed invention.

None of the five cited references alone or in combination render the instant invention obvious.

VIII. ALVING

US 5,820,880 to Alving et al ("Alving") is cited by the Examiner as teaching that Tweens are liposomal stabilizers as being "of interest." Applicants' note that the "stabilizing effect" of Tween is required only in the unstabilizing presence of alum containing liposomes as viewed by Alving et al. Alving, col. 2, line 60 to col. 3, line 7. Further comment is deemed unnecessary.

IX. FOREIGN REFERENCES

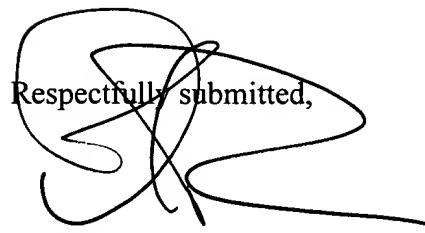
The requested Foreign references will be promptly provided as requested.

X. FEES

One dependent claim has been added and 39 claims canceled. No additional claim fees are believed due.

CONCLUSION

Allowance of the present claims is requested.


Respectfully submitted,

David L. Parker
Reg. No. Reg No. 32,165
Attorney for Applicants

ARNOLD WHITE & DURKEE
P.O. Box 4433
Houston, Texas 77210-4433
(512) 418-3000

Date: June 17, 1999